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EXAMINER	
DOWELL, PAUL THOMAS	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/517,663	AKIRA, SHIZUO	
	Examiner	Art Unit	
	Paul Dowell	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *8-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/13/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of claims 1-7 (group I) in the response on 4/24/2006 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/24/2006.

The restriction requirement of 4/4/2006 is made FINAL.

Claims 1-7 are under examination in the instant office action.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been placed of record in the file.

Information Disclosure Statement

The information disclosure statement filed 12/13/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Reference A6 appears to

be an article written in the Japanese language, a copy has not been provided and this specific reference has not been considered. A line has been drawn through this reference on the enclosed IDS.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5 and 6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 52 of copending Application No. 09/889,324 in view of Thoma-Uszynski et al **(Science, 291:1544-1547, 2001)**. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claim 52 of '324 is drawn to a mouse comprising a disruption of the Toll-Like Receptor (TLR) 2 gene, wherein said disruption results in no production of TLR2 protein, wherein said mouse exhibits the phenotype of being unresponsive to a bacterial cell component and wherein said bacterial cell component is a lipoprotein/lipopeptide. Claim 1 of the instant application is drawn to a non-human animal model non-responsive to mycobacterial lipoproteins/lipopeptides, wherein the function of the gene encoding a protein specifically recognizing mycobacterial lipoproteins/lipopeptides is disrupted, wherein the non-human animal is a rodent (claim 5), wherein the rodent is a mouse (claim 6).

The "mycobacterial lipoproteins/lipopeptides" recited in claim 1 of the instant application are encompassed by the lipoprotein/lipopetide bacterial cell component of claim 52 of '324 (further evidenced by the recitation of claim 65 of '324, "Mycobacterium tuberculosis lysate as a bacterial cell component"). In other words, mycobacterium are a species of the bacteria genus. The "TLR2 gene" recited in claim 52 of '324 is encompassed by the "gene encoding a protein specifically recognizing mycobacterial lipoproteins/lipopeptides" of claim 1 of the instant application. Thoma-Uszynski teach that the TLR2 gene is required for responsiveness to a 19-kD mycobacterial lipoprotein (e.g. page 1545: col. 1, paragr. 2 to col. 3, line 5; Fig. 1B). As such, the claims are drawn to inventions that overlap in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

Claim 4 is objected to because of the following informalities: the term TLR1 should be spelled out at the first recitation of said term (i.e. Toll-Like Receptor 1). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A transgenic mouse wherein the genome of said mouse comprises a homozygous inactivation of the TLR1 gene, wherein said TLR1 gene encodes a polypeptide that recognizes triacylated mycobacterial lipoproteins, wherein peritoneal macrophages of said mouse exhibit decreased responsiveness to said triacylated mycobacterial lipoproteins, wherein said peritoneal macrophages also comprise a homozygous disruption of the TLR1 gene;

and while being enabling for:

A transgenic mouse wherein the genome of said mouse comprises a homozygous inactivation of the TLR2 gene, wherein said TLR2 gene encodes a polypeptide that recognizes triacylated or diacylated mycobacterial lipoproteins, wherein peritoneal macrophages of said mouse exhibit decreased responsiveness to said mycobacterial lipoproteins, wherein said peritoneal macrophages also comprise a homozygous disruption of the TLR2 gene;

does not reasonably provide enablement for:

Any non-human animal wherein the genome of said mouse comprises a disruption of any gene encoding any protein that recognizes any mycobacterial lipoprotein, said disruption rendering said animal non-responsive to any mycobacterial lipoprotein.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of

working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of claim 1 is such that is encompasses any non-human animal that lacks the function of a gene that encodes any protein that recognizes any mycobacterial lipoproteins/lipopeptides. Claims 2 and 3 further limit the protein to recognizing any synthetic tri-acylated lipopeptides and to recognizing synthetic N-palmitoyl-S-dilaurylclyceryl, respectively. Claims 4 and 7 further limits the gene to that encoding TLR1 protein. Claims 5 and 6 further limit the animal to a rodent and a mouse, respectively.

The specification discloses: production of a TLR1 knockout mouse and production of a TLR2 knockout mouse (pages 19-20); preparation of thioglycollate-stimulated peritoneal macrophages from wild type mice, TLR1 knockout mice and TLR2 knockout mice (page 21); a response (i.e. production of the inflammatory cytokines TNFα and IL-6) from macrophages of wild type mice when said macrophages are exposed to the 19-kD lipoprotein from Mycobacterium tuberculosis while macrophages from TLR1 knockout mice exhibited a blunted response (i.e. comparatively less

production of TNFα) when treated as such (pages 21-22); blunted response from macrophages of TLR1 knockout mice when said macrophages are exposed to the synthetic triacylated peptide Pam_3CSK_4 (page 23); and blunted response from macrophages of TLR1 knockout mice when said macrophages are exposed to several synthetic triacylated synthetic peptides including Myr_3CSK_4, Lau_3CSK_4, N-Pam-S-Lau_2CSK_4 (i.e. N-palmitoyl-S-dilaurylglyceryl) and JBT3002 (pages 24-26).

First, the instant claims read on an animal wherein the function of any gene, encoding any protein recognizing any mycobacterial lipoprotein/lipopeptide (claim 1) or any synthetic triacylated lipopeptide (claim 2), is deleted. Further, claims 4 and 7 read on an animal non-responsive to any mycobacterial lipoprotein/lipopeptide wherein the function of the gene encoding TLR1 is deleted.

The specification discloses that peritoneal macrophages from TLR1 knockout mice exhibit a blunted response, compared to that of peritoneal macrophages from wild type mice, when challenged with triacylated mycobacterial lipoproteins/lipopeptides (i.e. when challenged with the 19-kD lipoprotein from Mycobacterium tuberculosis or the synthetic triacylated lipopeptides Pam_3CSK_4 Myr_3CSK_4, Lau_3CSK_4 or N-Pam-S-Lau_2CSK_4). The specification discloses that peritoneal macrophages from TLR1 knockout mice did not exhibit a blunted response when challenged with the diacylated lipopeptide MALP-2 (page 23 and Figure 9). Thus, the instant specification discloses that macrophages from TLR1 knockout mice respond normally to diacylated lipopeptides while TLR1 is required for a normal response to triacylated mycobacterial lipoproteins.

The art of record at the time of the invention teaches ligands that are bound to several TLR family members. Regarding TLR1: Takeuchi et al **(The Journal of Immunology, 169:10-14, 2002)** teaches generation of a TLR1 knockout mouse and that macrophages from the TLR1 knockout mice are defective in cytokine production in response to: the native mycobacterial 19-kD lipoprotein (page 11, col. 2, paragr. 3 to page 12, line 23); the synthetic tri-acylated lipoprotein Pam_3CSK_4 (page 12, col. 2, lines 4-6); and N-palmitoyl-S-dilaurylglyceryl (termed M-Pam-S-Lau_2CSK_4 by Takeuichi; page 13, col. 1, paragr. 1, lines 15-19); but not the diacylated lipoprotein MALP-2 (page 13, Figure 3B). Regarding TLR2: Thoma-Uszynski et al **(Science, 291:1544-1547, 2001)** teaches a TLR2 knockout mouse with impaired macrophage reactivity toward the 19-kD mycobacterial lipoprotein (page 1545: col. 1, paragr. 2 to col. 3, line 5). Further, Takeuchi **(International Immunology, 13:933-940, 2001)** teaches TLR2 knockout mice and that said mice exhibit impaired macrophage reactivity toward synthetic tri-acylated Pam_3CSK_4 lipopeptide (page 935, col. 2, paragr. 2, lines 31-35) and the diacylated lipoprotein MALP-2 (page 935, col. 2, paragr. 2). Regarding TLR6: Takeuchi **(International Immunology, 13:933-940, 2001)** teaches TLR6 knockout mice and that said mice exhibit impaired macrophage reactivity toward MALP-2 but not toward the synthetic tri-acylated Pam_3CSK_4 lipopeptide (page 935, col. 2, paragr. 2). Thus, the specification and the art of record at the time of the invention teach that TLR1 recognizes only triacylated lipoproteins, TLR6 recognizes only diacylated lipoproteins, while TLR2 recognizes both triacylated and diacylated lipoproteins.

Neither the specification nor the art of record teach any other naturally occurring or synthetic mycobacterial lipoproteins/lipopeptides that are recognized by TLR1. Even if there were teachings based on *in vitro* data (e.g. overexpressing TLRs in cultured cells) indicating that other lipoproteins/lipopeptides are recognized by TLR1, the art of record at the time of the invention teaches that such data is not a reliable indicator of biologically relevant TLR1 ligands. For example, Takeuchi **(International Immunopharmacology, 1:625-635, 2001)** teaches:

> It is not clear why more than 10 TLRs are encoded in the human genome. Further investigation of the function of TLRs other than TLR2 and TLR4 will clarify the entire mechanism of innate immune recognition. However, results from cells overexpressing TLRs sometimes mislead us as to the biological role of the molecule. We believe that the data based in overexpression experiments should be interpreted carefully. There is no doubt that a gene targeting strategy is a potent way to analyze the function of these receptors. (page 632: col. 1, paragr. 2 to col. 2, line 2)

Identifying ligands for TLRs is further made unpredictable by contamination of purified components. For example, Takeuchi also teaches that:

> It is of note that when purified bacterial component preparations were used to investigate the TLR responsible, one should interpret the results carefully not to misread the effect of contaminating reagent. We believe that the usage of synthetic compounds, which mimic the structures of PAMPs, is the best way to prevent misunderstanding. (page 630, col. 1, paragr. 1, lines 9-15)

The instant issue is whether macrophages from TLR1 knockout mice would exhibit a blunted response when challenged with <u>any</u> mycobacterial lipoprotein (i.e. monacylated or diacylated in addition to triacylated mycobacterial lipoproteins). Cole **(Nature, 393:537-544, 1989)** teaches that it was known at the time of the invention that the *Mycobacterium tuberculosis* genome comprised genes encoding ~90 lipoproteins, "some of which are enzymes or components of transport systems" (page 542, col. 2, paragr. 1, lines 9-13) that are unlikely to elicit either an inflammatory response or

antigenic response either in a TLR1-dependent or TLR1-independent manner; although Cole does not teach the acylation state of each of said lipoproteins. It is noted, however, that the breadth of the instant claims read on each and every one of the ~90 lipoproteins taught by Cole. Further, Takeuchi **(International Immunology, 13:933-940, 2001)** teaches that "[A] monacylated lipopeptide failed to induce TNF-a production even in wild type macrophages (data not shown), indicating that the type of lipid moiety determines activation of host macrophages" (page 935, col. 2, paragr. 2, lines 11-14). Neither the art of record nor the specification provides any guidance or evidence to indicate that any TLR, including TLR1, binds to or mediates a response from said ~90 lipoproteins taught by Cole. Further, the instant specification discloses that TLR1 specifically recognizes only triacylated mycobacterial lipoproteins. Neither the art of record nor the specification provides evidence that TLR1 would recognize or mediate a response from any other type of mycobacterial lipoprotein (e.g. monacylated or diacylated) other than triacylated mycobacterial lipoproteins.

Second, claims 1-4 and 6 read on any non-human animal. Claim 5 reads on any rodent. The specification discloses only the generation of transgenic mice. The specification discloses generation of said mice by homologous recombination in embryonic stem (ES) cells. Neither the specification nor the art of record at the time of the invention are enabling for generating any gene targeted/knockout animals other than mice. For example, Houdebine **(Journal of Biotechnology, 98:145-160, 2002)** teaches that mouse was the only species for which ES cell technology was available to

successfully create gene targeted/knockout animals. Specifically, when considering gene transfer using embryonic cells, Houdebine teaches:

> Despite repeated efforts, ***the extension of this method to species other than mouse failed***. This is clearly due to the fact that the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line. For years, it was admitted that mouse was the model for the use of ES cells to mutate genes in a targeted manner. ***The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow*** now inclines to consider that the so-called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course. They might contribute to define conditions to use ES cells and chimeric animals to replace genes in various species. (page 149, col. 1, paragr. 1; emphasis added)

Similarly, Smith **(Journal of Biotechnology, 99:1-22, 2002)** teaches that mouse was the only species for which technology was available to successfully create gene targeted/knockout animals:

> ***ES cell technology has enabled a large range of transgenic approaches in the mouse***. Types of gene modifications presently available in the mouse include targeted elimination of endogenous gene expression (gene 'knockout'), targeted gene repair/replacement, conditional gene targeting and 'gene trap' reporter systems.
>
> ***The use of ES cells is limited due to the fact that, to date, the mouse is the only animal from which ES cell lines have been unequivocally established***. It would be surprising if this limitation represents a fundamental biological barrier. However, ***further empirical work is needed before true ES cell lines become available for other species***. It is possible that the inbred strains of mice used to generate ES cells may carry mutations that are essential for the generation of ES cells. If such mutations represent a precondition for ES cell derivation, then it may take a considerable amount of time to establish nonmurine ES cell lines. Nevertheless, major progress has recently, been made in the analysis of molecular pathways of ICM and trophoblast differentiation in mammals. Such progress is expected to have a positive impact on nonmurine ES cell establishment. ***When nonmurine ES cells become available, the established mouse technologies will provide the basis for in vitro genetic modification of all species***. (page 3: col. 1, paragr. 3 to col. 2, line 11; emphasis added)

Thus, neither the specification nor the art of record at the time of the invention provide enabling support for the breadth of the instant claims which encompass any non-human animal.

Third, the instant claims read on animals comprising both heterozygous and homozygous deletions of the gene encoding a protein specifically recognizing the recited lipoproteins/lipopeptides. However, the specification discloses phenotypes only from mice comprising homozygous deletions of the TLR1 and TLR2 genes. Similarly, the art of record at the time of the invention discloses phenotypes only from mice comprising homozygous deletions of the TLR2 and TLR6 genes. Neither the specification nor the art of record at the time of the invention provide evidence that mice comprising heterozygous deletions in any TLR gene would have a phenotype.

In summary, an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate in scope with the instant claims. Such experimentation will be undue because of the unpredictability of any one TLR recognizing or mediating a response to any mycobacterial lipoprotein, the unpredictability of generating any transgenic animals other than mice and the unpredictability of the phenotype of animals comprising heterozygous deletions in any one TLR gene. Neither the specification nor the art of record at the time of the invention provides sufficient guidance to address these issues for an artisan to practice the claimed invention.

Thus, limiting the scope of the claims to:

A transgenic mouse wherein the genome of said mouse comprises a homozygous inactivation of the TLR1 gene, wherein said TLR1 gene encodes a polypeptide that recognizes triacylated mycobacterial lipoproteins, wherein peritoneal macrophages of said mouse exhibit decreased responsiveness to said triacylated mycobacterial lipoproteins, wherein said peritoneal macrophages also comprise a homozygous disruption of the TLR1 gene;

and while being enabling for:

A transgenic mouse wherein the genome of said mouse comprises a homozygous inactivation of the TLR2 gene, wherein said TLR2 gene encodes a polypeptide that recognizes triacylated or diacylated mycobacterial lipoproteins, wherein peritoneal macrophages of said mouse exhibit decreased responsiveness to said mycobacterial lipoproteins, wherein said peritoneal macrophages also comprise a homozygous disruption of the TLR2 gene, is proper.

Written Description

Claims 1-3, 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The breadth of claim 1 is such that is encompasses a non-human animal that lacks the function of any gene that encodes any protein that recognizes any

mycobacterial lipoproteins/lipopeptides. Claims 2 and 3 further limit the protein to recognizing any synthetic triacylated lipopeptides and to recognizing synthetic N-palmitoyl-S-dilaurylclyceryl, respectively. Claims 4 and 7 further limits the gene to that encoding TLR1 protein. Claims 5 and 6 further limit the animal of claim 1 to a rodent and a mouse, respectively.

When claims 1-3, 5 and 6 are analyzed in light of the specification, instant invention encompasses a very large genus of animals comprising disruptions in a large number of genes that encode a large number of proteins that recognize a large number of mycobacterial lipoproteins/lipopeptides and/or synthetic triacylated lipopeptides. However, the specification only discloses two of the claimed animals: a TLR1 knockout mouse and a TLR2 knockout mouse.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only two of the claimed animals are described (i.e. a TLR1 knockout mouse and a TLR2 knockout mouse). While the genus encompasses a very large number of animals, the specification does not describe the complete structure of a representative number of species.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, there is no other identifying characteristic of the claimed large genus of animals

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Further, Applicant's attention is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In conclusion, Applicant's disclosure of two species of the claimed broad genus is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the claimed broad genus at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 recite, "wherein the function of the gene...is deleted on its chromosome". Nucleic acids comprised within genes of chromosomes are deleted when carrying out standard genetic recombination techniques. It is not clear how a function of a gene is deleted nor is it clear what is meant by said recitation. Further to what the recitation "its chromosome" is referring is not clear. For example, is "its" referring to the

animal or to the chromosome from which the targeted gene is located? Said recitations are generally unclear. Claims 3-6 depend directly or indirectly from claims 1 or 2 and likewise are rejected.

Claim 7 recites, "wherein the TLR1 gene function is deleted into the mouse blastocysts". As put forther herein above, function is not typically deleted, rather nucleic acids comprised within genes are deleted. Further, it is not clear what is intended by "deleted into the mouse blastocyst".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Takeuchi et al **(The Journal of Immunology, 169:10-14, 2002)**.

Takeuchi teaches generation of a TLR1 knockout mouse (page 10, col. 3, paragr. 3 to page 11, col. 1, line 11; page 11, col. 2, paragr. 2). Takeuchi teaches that macrophages from TLR1 knockout mice are defective in cytokine production in response to: the native mycobacterial 19-kD lipoprotein (page 11, col. 2, paragr. 3 to page 12, line 23); the synthetic tri-acylated lipoprotein Pam_3CSK_4 (page 12, col. 2, lines

4-6); and N-palmitoyl-S-dilaurylglyceryl (termed M-Pam-S-Lau_2CSK_4 by Takeuichi; page 13, col. 1, paragr. 1, lines 15-19). Thus, Takeuich anticipates the instant claims.

It is noted that the instant rejection is put forth because the Takeuchi reference has a 102(a) date availability due to the foreign priority document not having been perfected. A certified English translation of the foreign priority document would remove the availability of the Takeuchi reference under 102(a) if all the claimed subject matter is in fact disclosed in the foreign priority document.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Alexopoulou et al **(Nature Medicine, 8:878-884, 2002)** as evidenced by Takeuchi et al **(The Journal of Immunology, 169:10-14, 2002)**.

Alexopoulou teaches generation of a TLR1 knockout mouse through homologous recombination in embryonic stem cells (page 880, col. 2, paragr. 5, lines 1-4; page 881, Fig. 5; page 883, col. 2, paragr. 1). Alexopoulou teaches that macrophages from TLR1 knockout mice are defective in cytokine production in response to the outer-surface lipoprotein of *Borrelia burgdorferi* (page page 881, col. 1, lines 2-3). Alexopoulou does not teach that TLR1 mice are defective in responding to mycobacterial lipoproteins or synthetic tri-acylated lipoproteins. However, Takeuchi teaches that macrophages from TLR1 knockout mice are defective in cytokine production in response to: the native mycobacterial 19-kD lipoprotein (page 11, col. 2, paragr. 3 to page 12, line 23); the synthetic tri-acylated lipoprotein Pam_3CSK_4 (page 12, col. 2, lines 4-6); and N-palmitoyl-S-dilaurylglyceryl (termed M-Pam-S-Lau_2CSK_4 by Takeuichi; page 13, col. 1, paragr. 1,

lines 15-19) and as such, these are inherent characteristics of the TLR1 knockout mouse. Thus, Alexopoulou anticipates the instant claims.

It is noted that the instant rejection is put forth because the Alexopoulou and Takeuchi references have a 102(a) date availability due to the foreign priority document not having been perfected. A certified English translation of the foreign priority document would remove the availability of the Alexopoulou and Takeuchi references under 102(a) if all the claimed subject matter is in fact disclosed in the foreign priority document.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Henneke et al **(Journal of Immunology, 167:7069-7076, 2001)**.

Henneke teaches a TLR1 knockout mouse (page 7070, col. 2, paragr. 3, lines 1-3). Thus, Henneke anticipates the insant claims.

It is noted that:

> When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. See MPEP 2112.01 and *In re Best,* 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claims 1, 2, 5 and 6 rejected under 35 U.S.C. 102(b) as being anticipated by Thoma-Uszynski et al **(Science, 291:1544-1547, 2001)** as evidenced by Takeuchi et al **(International Immunology, 13:933-940, 2001)**.

Thoma-Uszynski teaches a TLR2 knockout mouse with impaired macrophage reactivity toward the 19-kD mycobacterial lipoprotein (page 1545: col. 1, paragr. 2 to col. 3, line 5). Thoma-Uszynski did not teach that the TLR2 knockout mouse was unresponsive to synthetic tri-acylated lipopeptides; however, Takeuchi teaches TLR2 knockout mice and that said mice exhibit impaired macrophage reactivity toward synthetic tri-acylated Pam_3CSK_4 lipopeptide (page 935, col. 2, paragr. 2, lines 31-35). Thus, non-responsiveness to both the 19-kD mycobacterial lipoprotein and the synthetic tri-acylated Pam_3CSK_4 lipopeptide are inherent characteristics of the TLR2 knockout mouse. Thus, Thoma-Uszynski anticipates the instant claims.

Conclusions

No claims are allowed.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment and provide any statements that might help to identify support for the claimed invention (e.g. if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Dowell whose telephone number is 571-272-5540. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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